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TITLE: Changes in Ovarian Stromal Function in Premenopausal Woman Undergoing
Chemotherapy for Breast Cancer

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14. ABSTRACT The objective of this pilot study is to identify if androgen levels are adversely affected by adjuvant chemotherapy for breast cancer and whether low androgen levels are correlated with the frequency and severity of fatigue, weight gain, psychological symptoms, vasomotor symptoms and libido. A longitudinal, descriptive design will be used with questionnaires completed and blood drawn from 20 premenopausal women at 4 time periods: baseline (before treatment), mid-treatment, immediate post-treatment and 6 months later. Questionnaires include the Female Sexual Function Index, Greene Climacteric Scale, Profile of Mood States, Schwartz Fatigue Scale and a menses diary. Data analysis will involve descriptive statistics and plots of the hormone levels over time as well as t-tests to examine changes in hormone levels. Correlational analysis will be done to look at the relationship of symptoms to hormone levels. We have currently enrolled 18 women, 9 who have completed all study components. If a connection between low levels of androgens and symptoms is found, androgen replacement may be a viable treatment option for breast cancer survivors.					
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Statement of Work

Introduction

I would like to update you on the progress made with the Department of Defense on the protocol “Changes in Ovarian Stromal Function and Associated Symptoms in Premenopausal women Undergoing Chemotherapy for Breast Cancer”. Final HSRRB and IRB approval was received 4/05 and recruitment began 6/1/05. The study is continuing under a no cost extension (year one approved April 2005; year two approved June 13, 2006). To date we have 18 women enrolled in the pilot with 9 of whom have completed all study components. The remaining 9 women continue to be enrolled and are proceeding through the study.

Task 1: Work with a collaborative team to develop protocol of pilot study “Changes in Ovarian Stromal Function in Premenopausal Women Receiving Chemotherapy for Breast Cancer” months 1 and 2

Task completed with HSRRB and IRB approval received 4/05.

Task 2: Attend mentoring sessions and educational meetings, months 2 through 24.

In the past year I have participated in several mentoring experiences. These include:

- Work with Dr. Lynn Hartmann and her research team on her Center of Excellence in Breast Cancer grant. I have attend bi-weekly meetings; participated in writing of articles and grant proposals and reports. I continue to work closely with the team of study coordinators and statistical team in the collection, clean-up and analysis of data as well as in management of the budget.
- Attended several educational meetings:
 - Monthly Oncology Nursing Society Meetings
 - Monthly Medical Oncology Society Meetings
 - NVivo class to learn the use of this qualitative analysis package
- Work with Dr. Jeff Sloan and team to address current issues related to the clinical significance of quality of life data. I participated in writing a manuscript that was published on this topic (listed under reportable outcomes).
- Collaboration with Drs. Jeff Sloan and Michele Halyard to co-sponsor with the Federal Drug Administration (FDA) an open-registration conference addressing the FDA guidance on patient reported outcomes (PROs). This conference, titled *FDA Guidance on Patient Reported Outcomes: Discussion, Dissemination, and Operationalization*, was held in Chantilly, Virginia February 23-25, 2006. There were 392 attendees. I participated in presentations addressing PRO measurement issues. Additionally, I led a group in the preparation of a manuscript on validity related to PROs. This will be submitted for publication along with the entire series of presentations made at this conference. The reference for this manuscript is:

- Frost MH, Reeves BB, Leipa AM, Stauffer JW, Hays RD. What is sufficient evidence for the reliability and validity of patient-reported outcome measures?

Task 3: Get approval for pilot study, set up systems to implement study, months 3 - 6

The timeline for the study was delayed. Initial Mayo Clinic IRB approval was obtained November 26, 2002. DOD IRB revisions were made and subsequently approved by Mayo Clinic IRB on 7/29/2003 and 7/6/2004. Responses to recommendations/considerations put forth by the HSRRB minutes of September 22, 2004 were approved by the DOD March 17, 2005 and subsequently by Mayo Clinic IRB March 2005. With the short interval between final approval and the original research end date of July 31, 2005 and the award expiration date of August 31, 2005, a no-cost study extension was submitted and approval was granted April, 2005. The number of qualified patients were such that accrual was not reached by the end of the first no-cost study extension. With the desire to complete study accrual, a second no-cost study extension was submitted. The second approval was granted June 13, 2006.

Task 4: Accrue to study, months 7 - 18

Accrual began June 1, 2005. Initial accrual difficulty resulted from eligible women deciding to have chemotherapy at their home institution. We were able to work with our laboratory to facilitate the patient blood draws at their home institution and mailed back to Mayo Clinic. We have accrued 18 women to the study to date: (a) 9 of these women have completed the study, (b) 6 have completed through the third data point, (c) 1 has completed through the second data point and (d) 2 have completed only the first data point (one who was started on a luteinizing hormone-releasing hormone agonist, thus, additional data will not be collected). Three of the enrolled women have had oophorectomies before study completion. Thirteen women eligible for participation refused study participation. We are in the process of submitting a protocol modification request to DOD and Mayo IRBs to allow recruitment of additional women to account for the surgical/medical interventions that interfere with our outcome measures.

Task 5: Data entry and analysis, months 19-24.

Data has been entered into a database as it is received.

Task 6: Final analysis and report writing, month 24

Data collection is still underway.

Task 7: Strategize follow-up study and program of research based on pilot data, month 24.

Data collection is still underway.

Key Accomplishments

- Addressed pre-review considerations included in the HSRRB minutes of September 22, 2004
- Approval by HSRRB March 17, 2005, pending completion of paperwork by Mayo's Institutional Official
- Approval of changes for HSRRB minutes of September 22, 2004 by Mayo Clinic IRB March, 2005
- Approval of a one year no-cost extension April 2005 (to extend research period to July 31, 2006)
- Study opened for accrual June 1, 2005
- Approval of a second one year no-cost extension June 2006 (to extend research period to July 31, 2007)
- Accrual of 18 patients into study as of August 28, 2006

Reportable Outcomes

- Reviewed manuscripts for *JAMA and Archives, Journal of Clinical Oncology, Cancer, Psycho-Oncology* as a means to enhance my knowledge regarding critical writing skills and publications.
- Attended a two day Nvivo class to learn this qualitative software package
- Publications in conjunction with
 - **Dr. Lynn Hartmann and colleagues**
 - Milanese TR, Hartmann LC, Sellers TA, **Frost MH**, Vierkant RA, Maloney SD, Pankratz VS, Degnim AC, Vachon CM, Reynolds CA, Thompson RA, Melton LJ, Good EL, Visscher DW. The impact of age-related lobular involution on breast cancer risk. Journal of the National Cancer Institute. 2006, provisionally accepted for publication.
 - Lewis JT, Hartmann LC, Vierkant RA, Maloney SD, Pankratz VS, Allers TM, **Frost MH**, Visscher DW. An Analysis of Breast Cancer Risk in Women with Single, Multiple, and Atypical Intraductal Papilloma. American Journal of Surgical Pathology 2006;30(6): 665-672.

- **Frost MH**, Slezak JM, Tran NV, Williams CI, Johnson JL, Woods JE, Petty PM, Donohue JH, Grant CS, Sloan JA, Sellers TA, Hartmann LC. Satisfaction after contralateral prophylactic mastectomy: The significance of mastectomy type, reconstructive complications, and body appearance. Journal of Clinical Oncology 2005;23(31): 7849-56
- Hartmann LC, Sellers TA, **Frost MH**, Lingle WL, Degnim AC, Ghosh K, Vierkant RA, Maloney SD, Pankratz VS, Hillman DW, Suman VJ, Johnson J, Blake C, Tlsty T, Vachon CM, Melton LJ, Visscher DW. Benign Breast Disease and Breast Cancer Risk in the Mayo Cohort Study. NEJM, 2005;353(3), 229-237.

Dr Jeff Sloan and colleagues

- Sloan JA, **Frost MH**, Berzon R, Dueck A, Guyatt G, Moinpour C, Sprangers M, Ferrans C, Cella D, Clinical Significance Consensus Meeting Group. The clinical significance of quality of life assessments in oncology: a summary for clinicians. Supportive Care in Cancer, Epub ahead of print, June 23, 2006.
- Brown P, Clark MM, Atherton P, Huschka M, Sloan JA, Gamble G, Girardi J, **Frost MH**, Piderman K, Rummans TA. Will improvement in quality of life (QOL) impact fatigue in patients receiving radiation therapy for advanced cancer? American Journal of Clinical Oncology 2006;29(1):52- 58.
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- Halyard M & **Frost MH**. The integration of quality of life assessments for clinical and research purposes. Current Problems in Cancer. 2006 In press.
- Rummans TA, Clark MM, Sloan JA, **Frost MH**, Bostwick JM, Atherton PJ, Johnson ME, Gamble G, Richardson J, Brown P, Martensen J, Miller J, Piderman K, Huschka M, Girardi J, Hanson J. Impacting quality of life for patients with advanced cancer with a structured multidisciplinary intervention: A randomized, controlled trial. Journal of Clinical Oncology. J Clin Oncol 2006 24(4):635-642.
- Halyard M, **Frost MH**, Sloan JA. Applying QOL assessments: Is the use of QOL data really any different than other medical testing? Current Problems in Cancer. 2006 In press.
- **Frost MH**, Huschka MM. Quality of Life from a Patient's Perspective -- Can We Believe the Patient? Applying QOL Assessments: Solutions for Oncology Clinical Practice and Research, Part 1. Current Problems in Cancer, 2(6):274-277.

Conclusions

I have had the opportunity to work with several researchers and their teams as a means to build my knowledge in regards to quality of life research, statistical procedures, team approaches to research, the article review process, manuscript preparation and submission, grant preparation and grant reports.

We have enrolled 18 of the 20 participants for this pilot study. However, before study completion 3 of these women had oophorectomies and one was started on a luteinizing hormone-releasing hormone agonist. I will be submitting a protocol modification to the Mayo Clinic IRB and DOD to allow recruitment of additional women to account for these interventions which interfere with our outcome measure.